REMARKS

Status of the Claims

By virtue of the Listing of Claims presented herein, claims 1-3, 5-12, and 14-21 are pending. Claims 7 and 15-21 were withdrawn in a previous response, without prejudice or disclaimer, as directed to non-elected subject matter. Claim 1 has been herein amended to omit the phrase, "...said PYY or...". The amendment is made without prejudice or disclaimer to the right to pursue non-elected or deleted subject matter in one or more continuation or divisional applications. Basis for the amendment may be found, for example, at page 11, lines 1 through 11, of patent application publication number WO 03/105763, which is the publication of corresponding international patent application number PCT/US03/18657, of which the instant application is a U.S. National Stage, which discloses, for example, that a PYY analog may be selected from a polypeptide having an active fragment of PYY. No new matter is introduced by way of the amendment.

Withdrawn Objections and/or Rejections

Applicants acknowledge the Examiner's withdrawal of the previous rejection of claims 1-3, 5, 10, and 13 under 35 U.S.C. § 102(a) as allegedly being anticipated by El-Salhy et al. (Peptides 23:397-402, February 2002), in view of Applicants' previous arguments.

Claim Rejections

Applicants have carefully considered the points raised in the outstanding Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejection under 35 U.S.C. § 112, first paragraph: written description

Claims 1-3, 5, 6, and 8-12 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner repeats the allegation that "[t]here is no disclosure of a defined relation between structure and

function of the PYY agonists. There is even no identification of any particular portion of the structure that must be conserved." (Office Action dated Sept. 5, 2007; page 4.) The Examiner continues, alleging that "the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed genus of PYY agonists." (Office Action dated Sept. 5, 2007; page 6.) For the reasons below, as well as those provided in previous responses, which are hereby incorporated by reference in their entireties, Applicants traverse.

As mentioned in previous responses, the standard for determining whether a claim drawn to a genus meets the written description requirement is clear. "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice. . . , reduction to drawings . . . , or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." See *Regents of the University of California v. Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406; M.P.E.P § 2163(II)(3)(a)(ii) (emphasis added).

What constitutes a "representative number" of species is an inverse function of the skill and knowledge in the art. *Capon v. Eshhar,* 418 F.3d 1349 (Fed. Cir. 2005). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Furthermore, description of a representative number of species does not require the description to be of such specifics that it would provide individual support for each species that the genus embraces: "That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *Falkner v. Inglis*, 448 F.3d, 1357, 1366 (Fed Cir. 2006). Furthermore, the

Federal Circuit has made clear that "*Eli Lilly* does *not* set forth a *per se* rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art. " *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006). "[T]here is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of **known** structure." *Falkner* at 1366 (emphasis added). Furthermore, "[n]one of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e.*, *Regents v. Lilly, Fiers v. Revel, Amgen*, or *Enzo Biochem*, require a re-description of what was already known." *Capon v. Eshhar*, 76 USPQ2d 1078 (Fed. Cir. 2005).

In this regard, and contrary to the Examiner's appraisal, the art at the time of the effective filing date of the instant application contained ample structural and functional information concerning PYY and PYY analogs as recited in the instant claims. Tellingly, the Examiner's own characterization of Balasubramaniam (U.S. Patent No.: 5,604,203) acknowledges that the PYY agonists and structure-function correlations provide therein, at least, were within the purview of the skilled artisan (see, e.g., Office Action dated September 5, 2007, page 9, last paragraph).

Additionally, Applicants note that Blundell et al. (1981) (submitted herewith) described the structure of the canonical PP fold, to atomic resolution, and identified secondary structural characteristics of the PP fold motif, including regions containing α-helical and β-sheet character, as well as specific residues and residue contacts involved in maintenance of PP fold integrity. Whereas the presence of the PP fold motif has been attributed to all members of the PP/NPY/PYY family of peptides (see, e.g., Keire et al., *Peptides*, pp. 314 (February 2002) (of record)) and particularly relevant for PYY structural integrity and activity (see, e.g., Keire et al., *Biochemistry* (2000) (of record)), additional structural determinants unique to numerous PYY and PYY analogs, and correlations of such determinants to PYY and PYY agonist function, were subsequently disclosed in the art (see, e.g., Keire et al., *Peptides*, (2002) (of record); Keire et al., *Am J. Physiol. Gastointest. Liver. Physiol* .(2000) (of record); U.S. Patent 5, 604,203 (of record); WO 03/026591 (of record); Bard *et al., J. Biol. Chem.* (1995) (submitted herewith); and Gehlert *et al.*, *Peptides* (1995) (submitted herewith)). Thus, numerous exemplary PYY and PYY agonists, their structures, and their associated receptor affinities, receptor selectivities, and

exemplary biological activities.

Thus, because numerous PYY agonists that are encompassed by the claimed methods were well within the purview of the skilled artisan at the time of the effective filing date of the instant application, it is clearly established that Applicants are under no requirement to provide an explicit re-disclosure of such species in order to satisfy the written description requirement. Indeed, such an explicit re-disclosure is unnecessary and irrelevant with respect to the written description requirement.

However, what is relevant to the analysis is the nature of the instant claims at issue, and the context of the genus within such claims. In this regard, Applicants reiterate that the instant claims are directed to various methods of treating an intestinal damage comprising administering a pharmaceutically active formulation of PYY or a PYY agonist to a human to treat the intestinal damage. Applicants also note that PYY(3-36), the sequence of which is designated as SEQ ID NO.:3, corresponds to human PYY(3-36), which displays 94% identity with respect to rat PYY. In this regard, the Examiner will appreciate that human PYY(3-36) constitutes an agonist of rat PYY; thus, the demonstration that human PYY(3-36) elicits the disclosed effects when administered to rat, as well as to rat islet cells or tissues, constitutes a *de facto* showing that a PYY agonist, as recited in the instant claims, is efficacious order to practice the instantly claimed methods. Therefore. as disclosed throughout the instant application, administration of PYY or a PYY agonist has an effect, for example to reduce intestinal damage, such as bowel atrophy, and to restore bowel mucosa or bowel function (see, e.g., paragraphs [0050] – [0063] and TABLE 1; FIGURE 2; and FIGURE 3).

Accordingly, the scope of the genus of PYY and PYY agonists is viewed in the context of the claimed methods, and the disclosure of species within the genus is understood by those skilled in the art based on the scope of teachings related to the claimed methods. In this regard, as in *Capon* and *Falkner (*see *supra)*, the Examiner will appreciate that the claims are not drawn to a novel genus of compounds, but rather to novel uses of a known set of compounds, as described above. Based on the scope of such teachings, the knowledge in the art, and the context of the claim invention, at least, more than adequate guidance as to structural and functional characterization of the PYY agonists useful in the claimed methods is provided to those skilled in the art to sufficient describe the invention commensurate in scope with the present claims.

Accordingly, PYY and PYY agonists useful in the claimed methods are sufficiently described in the specification so to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the therapeutic methods of the claimed invention.

Accordingly, the Section 112 rejection is in error and should be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 2, 5, and 10-12 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Balasubramaniam (U.S. Patent No. 5, 604, 203), hereinafter '203. Specifically, the Examiner maintains the assertion that "because Balasubramaniam teaches treating gastrointestinal disorders, especially infectious or inflammatory diarrhea, or diarrhea resulting from surgery", and because inflammatory diarrhea allegedly includes Crohn's disease, an alleged form of inflammatory bowel disease, with PYY and its analogues, the reference allegedly teaches administering PYY to a subject to treat intestinal damages associated with these diseases. For the reasons previously made of record, which are herein incorporated by reference in their entirety, as well as the reasons set forth below, traverse.

As mentioned in previous responses, it is well established that to anticipate a claim, a reference must disclose every element of the claim. *Verdegaal Bros. v. Union Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987) and In re Donohue, 766 F.2d 531, 534, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). Further, the absence of a single claimed element from a cited reference precludes a finding of anticipation. Atlas Powder Company v. E.I. du Pont de Nemours, 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). For the reasons previously made of record, which are herein incorporated by reference in their entirety, as well as the reasons set forth below, Applicant submits that cited prior art fails to disclose each and every element of the present claims, and therefore does not anticipate the instant claims.

As mentioned in previous responses, and contrary to the Examiner's repeated characterization of the reference, '203 does not teach or suggest a method of treating intestinal damage, or a method of treating intestinal damage associated with any of the conditions alleged by the Examiner to be taught in the reference. As mentioned in previous responses, the reference fails to provide any nexus between the alleged teaching of treating gastrointestinal disorders and

treating the damage caused by such disorders *per se*. Indeed, the reference fails to teach or suggest that, as a result of treating any of the conditions as allegedly disclosed in the reference, any intestinal damage caused by such disorders would also be treated as recited in the instant claims and as taught in Applicants' disclosure. In this regard, the Examiner is reminded that in order to put forth a rejection based on anticipation in view of an alleged prior invention, the alleged identical invention must be shown in complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989). Because, at least, '203 fails to teach the efficacious treatment of intestinal damage that is inflicted by gastrointestinal discorder *per se*, the reference does not teach all elements of the instantly claimed methods. Accordingly, the § 102(b) is in error and should be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner has again rejected claim 14 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Balasubramaniam (U.S. Patent No. 5, 604, 203), hereinafter '203, as applied to claims 1, 2, 5, and 10-12 above, and further in view of Dumont et al. 26:320-324 (1994). Specifically, the Examiner asserts that whereas '203 allegedly teaches a method of treating intestinal damage comprising administering a pharmaceutically active formulation of PYY or a PYY agonist to a human as applied to claims 1, 2, 5, and 10-12 above, '203 fails to teach the method of claim 14, comprising administering PYY[3-36]. The Examiner applies Dumont et al. in an attempt to cure the deficiencies of '203. Applicant respectfully traverses.

For the reasons provided above, at least, '203 fails to teach a method of treating intestinal damage that might result from a gastrointestinal disorder, per se, comprising administering a pharmaceutically active formulation of PYY or a PYY agonist polypeptide as instantly claimed. That Dumont et al. may teach that a PYY agonist, PYY[3-36], binds PYY receptors, as the Examiner contends, fails to cure the deficiencies of '203. Similar to that mentioned above, no nexus is provided linking alleged binding to PYY receptors to a method of treating intestinal damage per se, or in treating intestinal damage associated with the a condition or disorder, comprising administering a PYY or a PYY agonist polypeptide to treat the intestinal damage, as instantly claimed.

The Examiner has rejected claim 1-3, 5, 10, and 13 under U.S.C. § 103(a) as being

allegedly unpatentable over El-Salhy et al (Peptides 23:397-402, February 2002). Specifically, the Examiner asserts that El-Salhy et al. teaches the following: "a decreased level of PYY in human patients with gastrointestinal disorders, including inflammatory bowel diseases (examples as Crohn's disease and ulcerative colitis; pages 398-399)"; that "changes in PYY in gastrointestinal disorders could be beneficial in clinical practice and in cases where PYY increase is desirable, diet that increases PYY synthesis and release can be followed, or a receptor agonist can be utilized"; that "infusion of PYY in dogs increases colonic absorption of water, Na, and Cl ions, and PYY or its analogue can be of use as clinical agents in intestinal malabsorption disorders or after bowel resection". While the Examiner acknowledges that the reference "do[es] not explicitly teach the instantly claimed method," the Examiner concludes that it would nonetheless "have been obvious to one having ordinary skill in the art at the time the invention was made to administer to a subject or a human patient after bowel resection or to treat a gastrointestinal disorders (sic), including inflammatory bowel diseases (such a ulcerative colitis) (sic) with a reasonable expectation of success." The Examiner continues, contending that "[o]ne would have been motivated to do so because of the teachings of El-Salhy et al. as stated immediately above. Applicants traverse.

As mentioned in previous responses, and similar to the references cited with respect to the Section 102 discussed above, the alleged teachings of El-Salhy et al. as fail to teach or suggest any nexus between "a decrease in PYY levels in patients with gastrointestinal disorders, including inflammatory bowel diseases" and a therapeutic benefit that might be achieved by administering PYY or a PYY agonist to such patients, and certainly doest not teach that such a benefit comprises the treating intestinal damage that is associated with such disorders. Whereas the reference allegedly hypothesizes that "changes in PYY in gastrointestinal disorders could (Applicant's emphasis) be beneficial in clinical practice and in cases where PYY increase is desirable, diet that increases PYY synthesis and release can be followed, or a receptor agonist can be utilized," such hypothesis fails to teach which particular changes (e.g., an increase, a decrease, etc.) would be beneficial in which particular "clinical practice," or how such particular changes might be exploited such that a therapy for such a "clinical practice" is achieved.

Indeed, the reference itself advertises the ambiguous, contradictory, and inconclusive nature of its alleged "teachings" throughout. For example, the reference opines that certain

"changes in PYY seem to be an adaptive response to certain such disorders", whereas in other disorders, such changes in PYY "appear to be primary and could be one of the etiologic factors of [such] disease[s]" (Abstract). Further, whereas "the concentration of PYY in tissue extracts …of patients with Crohn's colitis and ulcerative colitis has been found to be lower than in controls (paragraph bridging pages 398 and 399)", "basal and postprandial plasma levels of PYY in these patients are elevated in patients (sic) with celiac disease" (page 399, second paragraph). Further still, whereas in one study performed in the author's laboratory "PYY cells have been found to be increased as compared to controls in the ascending colon of patients with CST [chronic idiopathic slow transit constipation]," another study performed in the same laboratory determined that "the number of colonic PYY cells has not been found to be affected," and whereas "the concentration of PYY in colonic tissue extracts from patients with CST has been reported to be high, basal and peak plasma PYY levels have been reported to be unaffected" (page 399, last paragraph).

> The confused nature of the report is perhaps most epitomized by its conclusion:
>
> The changes in PYY could be favorable in some intestinal disorders…[o]n the other hand, it could be harmful. The accumulated data of the changes in PYY in gastrointestinal disorders could be beneficial in clinical practice. Thus, in cases where PYY increase or decrease is desirable, diet that increases of decreases PYY synthesis and release can be used, or a receptor agonist or antagonist can be utilized.
> (page 402, last paragraph)

At best, the teachings of the reference merely reports the discordant aspect of the data accumulated with respect to PYY activity as it related to gastrointestinal disorders, and offers a invitation to rationalize this data such that a cohesive understanding as to PYY action in relation to the various "clinical practices" discussed might be achieved. It is simply a wish to invent.

The Examiner's assertion that the alleged teaching that infusion of PYY in dogs increases colonic absorption of water, Na, and Cl ions is similarly unavailing, insofar as, at least, the dogs in the study did not have an intestinal damage associated with an inflammatory bowel disease (see references [38] and [39] as cited in El-Salhy et al.). Thus, this alleged teaching simply fails to offer any nexus between water and nutrient absorption in healthy doges and a method of treating any disorder or condition whatsoever. Therefore, and particularly in light of the contradictory and ambiguous nature or the data reported throughout the remainder of the

reference, as mentioned above, this study certainly fails to teach or suggest to teach or suggest a method of treating intestinal damage comprising administering a pharmaceutically active formulation of PYY or a PYY agonist to a human in order to treat the intestinal damage, wherein said PYY or said PYY agonist is a polypeptide that comprises an active fragment of PYY, as instantly claimed.

The Examiner is further reminded that the Examiner must treat all aspects of the disclosure of a cited reference as a whole. As described above, in light of the contradictory, ambiguous, and vaguer nature of the reference, and its failure to provide any nexus between an alleged ability to treat any disorder with PYY or a PYY agonist and an ability to efficaciously treat intestinal damage associated with such disorder, the reference fails to provide any explicit or implicit teaching that would render obvious the instant claims. Accordingly, the Section 103(a) rejection is in error and should be withdrawn.

Objection to Claim 1

The Examiner objects to Claim 1 because "it recites 'wherein said PYY or said PYY agonist is a peptide that comprises an active fragment of PYY'. Since PYY necessarily comprises an active fragment of PYY, the limitation 'wherein said PYY is a peptide that comprises an active fragment of PYY' is not necessary."

Without acquiescing to the Examiner's objection, Applicant has amended the claim such that the claim recites:

1. A method of treating an intestinal damage comprising administering a pharmaceutically active formulation of PYY or a PYY agonist to a human to treat the intestinal damage, wherein said PYY agonist is a peptide that comprises an active fragment of PYY.

The amendment is made without prejudice or disclaimer to the right to pursue non-elected or omitted subject matter in one or more continuing or divisional applications.

Applicants submit that the amendment renders the Examiner's objection moot.

Conclusion

In conclusion, all rejections and objections outlined in the outstanding Office Action are in error and should be withdrawn.

Applicants believe that all issues raised in the Office Action have been properly addressed in this response and in the amendments to the claims as shown in the attached Listing of Claims. Accordingly, reconsideration and allowance of the amended claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the examiner is encouraged to contact Applicants' representative at the telephone number below.

No additional fees are believed due for this submission. However, if a fee is due, the Commissioner is hereby authorized to charge payment of any fees associated with this communication, to Applicant's Deposit Account No. 010535 referencing Docket No. 0402US-UTL. Additionally, the Commissioner is hereby authorized to charge payment or credit overpayment of any fees during the pendency of this application to Applicant's Deposit Account No. 010535.

Date: December 19, 2007

Respectfully submitted,

AMYLIN PHARMACEUTICALS, INC.

/Michael D. Ruse, Jr./
Michael D. Ruse, Jr.
Reg. No. 55,900

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
San Diego, California 92121
Phone (858) 552-2200
Facsimile (858) 552-1936